

10/500424

DT04 Rec'd PCT/PTO 28 JUN 2004

APPENDIX A

CHOATE, HALL & STEWART

A PARTNERSHIP INCLUDING PROFESSIONAL CORPORATIONS

EXCHANGE PLACE

53 STATE STREET

BOSTON, MASSACHUSETTS 02109-2804

TELEPHONE (617) 248-5000 • FAX (617) 248-4000

WWW.CHOATE.COM

TRANSMITTAL SHEET

Number of pages being sent 29 (including this page)

DATE 10 October 2003

Recipient	Company	Fax No.	Phone No.
1.	European Patent Office (IPEA/EP) Erhardtstr. 27 D-80331 Munich, GERMANY	011 49 89 2399 4465	011 49 89 2399 0

FROM: Nancy J. Hough, Foreign Filing Specialist

DIRECT DIAL: 617-248-5188

REMARKS:

Applicant: Eisai Co. Ltd.
Intl. Appln. No.: PCT/US02/40744
Intl. Filing Date: 18 December 2002
Priority: U.S.S.N. 60/343,678 filed 28 December 2001
For: LUMINACIN ANALOGS AND USES THEREOF

Please see the attached response to the Written Opinion dated 11 August 2003.

TIME SENT: _____ **OPERATOR:** _____ **CLIENT NO.** 2003946-0022

Return by: Inter-office Mail N. Hough/34 Hold for pick-up _____

THIS TRANSMITTAL IS INTENDED ONLY FOR THE USE OF THE INDIVIDUAL OR ENTITY TO WHICH IT IS ADDRESSED, AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND EXEMPT FROM DISCLOSURE UNDER APPLICABLE LAW. IF THE READER OF THIS TRANSMITTAL IS NOT THE INTENDED RECIPIENT, OR THE EMPLOYEE OR AGENT RESPONSIBLE FOR DELIVERING THE TRANSMITTAL TO THE INTENDED RECIPIENT, YOU ARE HEREBY NOTIFIED THAT ANY DISSEMINATION, DISTRIBUTION OR COPYING OF THIS COMMUNICATION IS STRICTLY PROHIBITED. IF YOU HAVE RECEIVED THIS COMMUNICATION IN ERROR, PLEASE NOTIFY US IMMEDIATELY.



Europäisches
Patentamt

European
Patent Office

Office européen
des brevets

Einsender / Sender / Expéditeur :

LAGNEAU, Nadege M.
CHOATE, HALL & STEWART
53 State Street
Exchange Place
Boston, Massachusetts 02109
UNITED STATES OF AMERICA

✉ D-80298 München
☎ (+49-89) 2399-0
Tx 523 656 epmu d
Fax (+49-89) 23 99-44 65
✉ P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
☎ (+31-70) 340-2040
Tx 31 651 epo nl
Fax (+31-70) 340-3016
✉ D-10958 Berlin
☎ (+49-30) 25901-0
Fax (+49-30) 25901-840

**Bestätigung über den
Eingang nachgereichter
Unterlagen für Patentan-
meldungen/Patente beim
Europäischen Patentamt**

Datum und Ort des Eingangs sind aus
der Perforation dieser Eingangsbestäti-
gung ersichtlich
(M + Datum = Einreichungsort München;
H + Datum = Einreichungsort Den Haag;
Datum + B = Einreichungsort Berlin)

**Acknowledgement of
receipt for subsequently
filed items relating to
patent applications/patents
at the European Patent
Office**

Date and place of receipt are shown by
the perforation appearing on this receipt
(M + date = Munich as place of receipt;
H + date = The Hague as place of receipt;
date + B = Berlin as place of receipt)

**Accusé de réception à
l'Office européen des bre-
vets de pièces produites
postérieurement au dépôt
d'une demande de brevet/
à la délivrance d'un brevet
européen**

La date et le lieu de réception sont indi-
qués par la perforation du présent accusé
de réception
(M + date = pièces reçues à Munich;
H + date = pièces reçues à La Haye;
date + B = pièces reçues à Berlin)

Eingereichte Unterlagen

Items filed

Pièces envoyées

Anmeldungs- (und Direktions-*) Nr./Patent Nr. Application (and Directorate*) No./Patent No. N° de la demande (et de la direction*)/n° du brevet	Ihr Zeichen Your reference Votre référence	ggfs. Art und Datum der Unterlagen** Nature and date of items (optional)** Nature et date des pièces (facultatif)**
1 PCT/US02/40744	2003946-0022	Response to Written Opinion (4 pp.)
2		Request for Amendment (3 pp.)
3		Appendix A (9 pp.)
4		Substitute sheets (10 pp.)
5		RRceipt for subsequently
6		filed items (2 pp.)
7		Fax Cover (1 p.)
8		
9		
10		

* falls bereits bekannt

* if already known

* si déjà connu

** Der Eingang der angegebenen Unterlagen
wird bestätigt.
Enthält diese Spalte keine Eintragungen, so
wird lediglich bestätigt, daß eine Sendung
zu dem angegebenen Aktenzeichen einge-
gangen ist.

** The receipt of the items indicated is
confirmed.
If this column does not contain any entries,
it is only confirmed that an item has been
received for the indicated file.

** La réception des pièces indiquées est
confirmée.
Faute de mention dans cette colonne, le
présent accusé de réception se rapporte à
une pièce quelconque envoyée sous la
référence indiquée.



Europäisches
Patentamt

European
Patent Office

Office européen
des brevets

Einsender / Sender / Expéditeur :

LAGNEAU, Nadege M.
CHOATE, HALL & STEWART
53 State Street
Exchange Place
Boston, Massachusetts 02109
UNITED STATES OF AMERICA

✉ D-80298 München
☎ (+49-89) 2399-0
Tx 523 656 epmu d
Fax (+49-89) 23 99-44 65

✉ P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
☎ (+31-70) 340-2040
Tx 31 651 epo nl
Fax (+31-70) 340-3016

✉ D-10958 Berlin
☎ (+49-30) 25901-0
Fax (+49-30) 25901-840

**Bestätigung über den
Eingang nachgereichter
Unterlagen für Patentan-
meldungen/Patente beim
Europäischen Patentamt**

**Acknowledgement of
receipt for subsequently
filed items relating to
patent applications/patents
at the European Patent
Office**

**Accusé de réception à
l'Office européen des bre-
vets de pièces produites
postérieurement au dépôt
d'une demande de brevet/
à la délivrance d'un brevet
européen**

Datum und Ort des Eingangs sind aus
der Perforation dieser Eingangsbestäti-
gung ersichtlich
(M + Datum = Einreichungsort München;
H + Datum = Einreichungsort Den Haag;
Datum + B = Einreichungsort Berlin)

Date and place of receipt are shown by
the perforation appearing on this receipt
(M + date = Munich as place of receipt;
H + date = The Hague as place of receipt;
date + B = Berlin as place of receipt)

La date et le lieu de réception sont indi-
qués par la perforation du présent accusé
de réception
(M + date = pièces reçues à Munich;
H + date = pièces reçues à La Haye;
date + B = pièces reçues à Berlin)

Eingereichte Unterlagen

Items filed

Pièces envoyées

Anmeldungs- (und Direktions-*) Nr./Patent Nr. Application (and Directorate*) No./Patent No. N° de la demande (et de la direction*)/n° du brevet	Ihr Zeichen Your reference Votre référence	ggfs. Art und Datum der Unterlagen** Nature and date of items (optional)** Nature et date des pièces (facultatif)**
1 PCT/US02/40744	2003946-0022	Response to Written Opinion (4 pp.)
2		Request for Amendment (3 pp.)
3		Appendix A (9 pp.)
4		Substitute sheets (10 pp.)
5		RRceipt for subsequently
6		filed items (2 pp)
7		Fax Cover (1 p.)
8		
9		
10		

* falls bereits bekannt

* if already known

* si déjà connu

** Der Eingang der angegebenen Unterlagen
wird bestätigt.
Enthält diese Spalte keine Eintragungen, so
wird lediglich bestätigt, daß eine Sendung
zu dem angegebenen Aktenzeichen einge-
gangen ist.

** The receipt of the items indicated is
confirmed.
If this column does not contain any entries,
it is only confirmed that an item has been
received for the indicated file.

** La réception des pièces indiquées est
confirmée.
Faute de mention dans cette colonne, le
présent accusé de réception se rapporte à
une pièce quelconque envoyée sous la
référence indiquée.

ATTORNEY DOCKET NUMBER: 2003946-0022 (VD 1207/PCT)

DT04 Rec'd PCT/PTO 28 JUN 2004

IN THE EUROPEAN PATENT OFFICE
AS INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

Applicant: Eisai Co. Ltd.
Intl. Appln. No.: PCT/US02/40744
Intl. Filing Date: 18 December 2002
Priority: U.S.S.N. 60/343,678 filed 28 December 2001

For: LUMINACIN ANALOGS AND USES THEREOF

VIA FACSIMILE
011-49-89-2399-4465
CONFIRMATION BY
INTERNATIONAL COURIER

EUROPEAN PATENT OFFICE
D-80298 MUNICH
GERMANY
Authorized Officer: Examiner

Dear Sir/Madam:

RESPONSE TO WRITTEN OPINION

This paper is submitted in response to the Written Opinion mailed 11 August 2003, for the above-identified application. The deadline for response to the Written Opinion is 11 October 2003; Thus Applicant respectfully submits that the filing of this response on 10 October 2003 is timely. Responsive to the Written Opinion Applicant respectfully submits the following Remarks.

Applicant thanks the Examiner for his/her careful consideration of this case, and requests that he/she reconsider his/her evaluation of the ability of the claims to satisfy the International Standards of Patentability in light of this Response.

The Opinion is based on the documents cited on the International Search Report (ISR) issued 28 March 2003, in particular the documents cited "X". The ISR cites the following references in category X:

1. Naruse *et al.*, "Luminacins: a family of capillary tube formation inhibitors from streptomyces sp. I. Taxonomy, fermentation, isolation, physico-chemical properties and structure elucidation" *Journal of Antibiotics, Japan Antibiotics Research Association, Tokyo, JP*, 53(6):579-590, 2000;

2. Wakabayashi, *et al.*, "Luminacins: a family of capillary tube formation inhibitors from streptomyces sp. II. Biological activities", *Journal of Antibiotics, Japan Antibiotics Research Association, Tokyo, JP*, 53(6):591-596, 2000;
3. Sharma, *et al.*, "UCS15A, a non-kinase inhibitor of Src signal transduction", *Oncogene, Basingstoke, Hants, GB*, 20(17): 2068-2079, 2001; and
4. Tatsuta, *et al.*, "The first total synthesis and establishment of absolute structure of luminacins C1 and C2", *Tetrahedron Letters*, 42(43), 7625-7628, 2001.

As detailed in the Request for Amendment under PCT Article 34 filed herewith, claims 1, 22 and 43, as amended, include the proviso that "when R_4 , R_5 , R_8 and R_{10} are each hydroxyl, R_{13} and R_{14} are each methyl, R_2 and R_3 , taken together, form an epoxide, R_7 is hydrogen and n is 1, the following groups do not occur simultaneously as defined:

- (i) R_1 is methyl, R_9 is hydrogen, (R_{11}, R_{12}) is (=O) and R_6 is ethyl or isopropyl;
- (ii) R_1 is methyl, R_9 is CHO, (R_{11}, R_{12}) is (OMe, H) and R_6 is ethyl, propyl or isopropyl;
- (iii) R_1 is methyl, R_9 is CHO, R_{11} and R_{12} are hydrogen and R_6 is ethyl, propyl or isopropyl;
- (iv) R_1 is methyl, R_9 is COCH₃, R_{11} and R_{12} are hydrogen and R_6 is ethyl; and
- (v) R_1 is ethyl, R_9 is CHO, R_{11} and R_{12} are hydrogen and R_6 is ethyl"

Therefore, claims 1, 22 and 43 specifically exclude:

Luminacins A ₁ , A ₂ , B ₁ , B ₂	[proviso (i)]
Luminacins C ₁ , C ₂ , E ₁ , E ₂ , E ₃	[proviso (ii)]
Luminacins D, G ₁ , G ₂	[proviso (iii)]
Luminacin H	[proviso (iv)]
Luminacin F	[proviso (i)]

Reference 1 (Naruse *et al.*) discloses Luminacins A₁, A₂, B₁, B₂, C₁, C₂, D, E₁, E₂, E₃, F, G₁, G₂ and H. As mentioned above, these luminacins are specifically excluded from the claimed invention. In addition, Reference 1 does not teach nor suggest any other luminacin analogs (*e.g.*, synthetic analogs), nor does it teach pharmaceutical compositions comprising luminacin analogs or a method of using them to treat cancer. Therefore, Reference 1 cannot

anticipate nor render obvious the presently claimed invention.

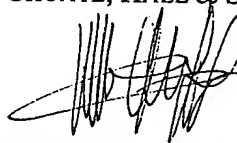
Reference 2 (Wakabayashi *et al.*) reports biological studies concerning naturally occurring luminacins. For example, Table 1 page 593 reports IC₅₀ values of Luminacins A₁, A₂, B₁, B₂, C₁, C₂, D, E₁, E₂, F, G₁ and H in assays for anti-angiogenesis and anti-proliferative activity. Again, these naturally-occurring luminacins are specifically excluded from the claimed invention. In addition, although Reference 2 teaches the anti-angiogenic activity of fourteen naturally occurring luminacins (*e.g.*, A₁ through H), it does not provide any teaching or guidance for any other luminacin analogs (*e.g.*, synthetic analogs), nor does it teach pharmaceutical compositions comprising luminacin analogs or a method of using them to treat cancer. Therefore, Reference 2 cannot anticipate or render obvious the presently claimed invention.

Reference 3 (Sharma *et al.*) reports Src-inhibitory effects of UCS15A by a mechanism that involves disruption of protein-protein interactions mediated by Src. According to Figure 1 on page 2070 of Reference 3, UCS15A is luminacin C₁ or C₂, which, as mentioned above, are specifically excluded from the invention, as claimed. In addition, Reference 3 does not teach nor suggest luminacin analogs other than luminacin C₁ and C₂ (*e.g.*, synthetic analogs), nor does it provide any suggestion or teaching for pharmaceutical compositions comprising such compounds or a method of using them to treat cancer. Therefore, Reference 3 cannot anticipate or render obvious the presently claimed invention.

Reference 4 (Tatsuta *et al.*) discloses luminacins C₁ and C₂ and synthetic intermediates thereof. As mentioned above, claims 1, 22 and 43 specifically exclude luminacin C₁ and C₂. In addition, claim 1 includes the proviso that "*when R₁ is methyl, R₂ and R₃, taken together, form an epoxide, R₆ is ethyl, R₇ is hydrogen, (R₁₁, R₁₂) is (OMe, H), R₁₃ and R₁₄ are each methyl and n is 1, the following groups do not occur simultaneously as defined: R₄ and R₅ is OH or OBn, R₈ and R₁₀ is OH or -OCH₂OCH₃ and R₉ is -CHO, -CH₂OH or -CH₂OTBS*" which specifically excludes the synthetic intermediates disclosed in Reference 4. Also, Reference 4 does not teach nor suggest luminacin analogs other than luminacin C₁ and C₂ (*e.g.*, synthetic analogs), nor does it provide any suggestion or teaching for pharmaceutical compositions comprising these compounds or a method of using them to treat cancer. Therefore, Reference 4 cannot anticipate or render obvious the presently claimed invention.

In light of the above Remarks, Applicant respectfully submits that all claims, as amended, meet the International Standards of Patentability. A favorable International Preliminary Examination Report is respectfully requested.

Respectfully Submitted,
CHOATE, HALL & STEWART



Nadège M. Lagneau, Ph.D.
Agent for Applicant

Dated: 10 October 2003

PATENT GROUP
CHOATE, HALL AND STEWART
Exchange Place
53 State Street
Boston, MA 02109
Tel: (617) 248-5000
Fax: (617) 248-4000

IN THE EUROPEAN PATENT OFFICE
AS INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

Applicant: Eisai Co. Ltd.
Intl. Appln. No.: PCT/US02/40744
Intl. Filing Date: 18 December 2002
Priority: U.S.S.N. 60/343,678 filed 28 December 2001

For: LUMINACIN ANALOGS AND USES THEREOF

VIA FACSIMILE
011-49-89-2399-4465
CONFIRMATION BY
INTERNATIONAL COURIER

EUROPEAN PATENT OFFICE
D-80298 MUNICH
GERMANY
Authorized Officer: Examiner

Dear Sir/Madam:

REQUEST FOR AMENDMENT UNDER PCT ARTICLE 34

1. Applicant respectfully requests authorization from the International Preliminary Examining Authority for amendment under PCT Article 34 and respectfully submits that the replacement sheets, as submitted herewith, reflect claim amendments which do not introduce new matter. Applicant submits herewith replacement sheets number 68, 69, 74-77 and 80-82, to replace sheets number 68, 69, 74-77 and 80-82, originally filed for this application.

2. In respect of each claim appearing in the international application based on replacement sheets 68, 69, 74-77 and 80-82 submitted herewith, and in accordance with PCT Section 205(b), the following claim(s) is/are:

- (i) Unchanged: Claims 2, 20, 21, 40-42 and 45-46 are unchanged;
- (ii) Replaced: Claims 1, 22-26 and 43 are replaced with new claims 1, 22-26 and 43, respectively;
- (iii) Canceled: Claim 44 is canceled.

A marked-up copy of Claim Replacements highlighting the changes is provided herewith as attached Appendix A. Deletions are represented in strikethrough, and additions

are represented in underlining.

Applicant respectfully submits that no new matter is presented with these amendments. Specifically, claim 1, as amended, includes recitation of the variable R_7 in the proviso (*i.e.*, “ R_7 is hydrogen” in proviso (a)), which sought to exclude the luminacins listed in the table bridging pages 1 and 2 of the specification, but was inadvertently omitted at the time of filing. In addition, claim 1, as amended, includes the proviso that “when R_1 is methyl, R_2 and R_3 , taken together, form an epoxide, R_6 is ethyl, R_7 is hydrogen, (R_{11} , R_{12}) is (OMe, H), R_{13} and R_{14} are each methyl and n is 1, the following groups do not occur simultaneously as defined: R_4 and R_5 is OH or OBn, R_8 and R_{10} is OH or $-OCH_2OCH_3$ and R_9 is $-CHO$, $-CH_2OH$ or $-CH_2OTBS$ ” which specifically excludes the synthetic intermediates disclosed in the Tatsuta *et al.* reference cited in the Written Opinion (*i.e.*, Reference 4).

Claim 22 has been amended to include recitation of the variable R_7 in the proviso (*i.e.*, “ R_7 is hydrogen”), which was inadvertently omitted at the time of filing.

Claims 23-26 have been amended to correct the structure by replacing “OR₅” with “R₅”. Support for this amendment can be found *inter alia* in original claims 2-5 and 45-48 where the structures are correctly depicted. Additional support can be found, for example, in original claim 33 in the recitation that R_5 (*e.g.*, in the structures of claims 23-26) is hydroxyl or lower alkoxy. Thus the oxygen atom is already taken into account in R_5 itself.

Claim 43, as amended, includes the proviso that “when R_4 , R_5 , R_8 and R_{10} are each hydroxyl, R_7 is hydrogen, R_{13} and R_{14} are each methyl, R_2 and R_3 , taken together, form an epoxide, and n is 1, the following groups do not occur simultaneously as defined:

- (i) R_1 is methyl, R_9 is hydrogen, (R_{11} , R_{12}) is (=O) and R_6 is ethyl or isopropyl;
- (ii) R_1 is methyl, R_9 is CHO, (R_{11} , R_{12}) is (OMe, H) and R_6 is ethyl, propyl or isopropyl;
- (iii) R_1 is methyl, R_9 is CHO, R_{11} and R_{12} are hydrogen and R_6 is ethyl, propyl or isopropyl;
- (iv) R_1 is methyl, R_9 is COCH₃, R_{11} and R_{12} are hydrogen and R_6 is ethyl; and
- (v) R_1 is ethyl, R_9 is CHO, R_{11} and R_{12} are hydrogen and R_6 is ethyl”. Support for this amendment can be found *inter alia* in original claim 44, now canceled.

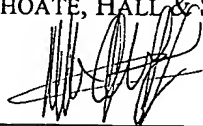
Applicant submits that the amendments to the claims, as described above and detailed herein, do not present new matter. Thus Applicant respectfully requests entry of these amendments, and consideration of these amendments in processing the application.

3. The deletion of any claims and any other loss of claimed subject matter is being made

solely to expedite prosecution of the subject matter now claimed, rather than in acquiescence to any positions taken by the Examiner. In fact, Applicant is *not* acquiescing to any of those positions and is submitting the present amendments without prejudice to the subsequent prosecution of claims to some or all of the subject matter which might be lost by virtue of this paper. Applicant additionally reserves the right to re-introduce the subject matter of any of the canceled claims, or subject matter which might be lost by virtue of amendments set forth in this paper, in the application.

Applicant hereby requests that the ISA begin its examination upon this submission. Favorable action is respectfully requested.

Respectfully submitted,
CHOATE, HALL & STEWART



Nadège M. Lagneau, Ph.D.
Agent for Applicant

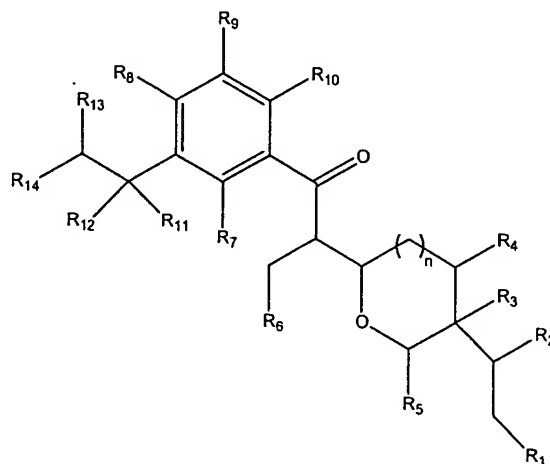
Dated 10 October 2003

PATENT GROUP
CHOATE, HALL & STEWART
Exchange Place
53 State Street
Boston, MA 02109
(617) 248-5150

- APPENDIX A -

VERSION WITH MARKINGS TO SHOW CHANGES MADE
CLAIM REPLACEMENTS

1. A compound having the structure:



and or pharmaceutically acceptable ~~derivatives~~ derivative thereof;

wherein n is 0, 1 or 2;

R₁ is hydrogen or an aliphatic, heteroaliphatic, aryl or heteroaryl moiety;

R₂ and R₃ are each independently hydrogen, or, when taken together, may be -O- or -
(CH₂)_q-, wherein q is 1, 2 or 3;

R₄ is hydrogen, hydroxyl, protected hydroxyl or ORⁱ, or an aliphatic or heteroaliphatic moiety,

wherein Rⁱ is an aliphatic or heteroaliphatic moiety;

R₅ is hydrogen, hydroxyl, protected hydroxyl or ORⁱⁱ, or an aliphatic or heteroaliphatic moiety,

wherein Rⁱⁱ is an aliphatic or heteroaliphatic moiety, or wherein R₁ and R₅, when taken together, may form a cycloaliphatic or heterocycloaliphatic moiety comprising 6 to 12 atoms;

R₆ is hydrogen, or an aliphatic, heteroaliphatic, aryl or heteroaryl moiety;

R₇ is hydrogen, hydroxyl, protected hydroxyl, ORⁱⁱⁱ, or an aliphatic or heteroaliphatic

moiety,

wherein R^{iii} is an aliphatic or heteroaliphatic moiety;

R_8 is hydrogen, hydroxyl, protected hydroxyl or OR^{iv} ,

wherein R^{iv} is an aliphatic or heteroaliphatic moiety;

R_9 is hydrogen, $-CF_3$, $-CHO$, imine, hydrazone, oxime, carboxylic acid, carboxylic ester, acyl halide, ketone, amide, acetal, anhydride, dihalide, epoxide, nitrile or an aliphatic or heteroaliphatic moiety;

R_{10} is hydroxyl or protected hydroxyl;

R_{11} and R_{12} are each independently hydrogen, hydroxyl or OR^v , or an aliphatic or heteroaliphatic moiety, or, when taken together, may be $-(C=O)-$;

wherein R^v is an aliphatic or heteroaliphatic moiety;

and R_{13} and R_{14} are each independently hydrogen, or an aliphatic, heteroaliphatic, aryl or heteroaryl moiety;

whereby each of the foregoing aliphatic and heteroaliphatic moieties may independently be substituted or unsubstituted, cyclic or acyclic, linear or branched, and whereby each of the foregoing aryl and heteroaryl moieties may be substituted or unsubstituted unsubstituted;

~~with the proviso that when R_4 , R_5 , R_8 and R_{10} are each hydroxyl, R_{13} and R_{14} are each methyl, R_2 and R_3 , taken together, form an epoxide, and n is 1, the following groups do not occur simultaneously as defined:~~

with the proviso that:

(a) when R_4 , R_5 , R_8 and R_{10} are each hydroxyl, R_7 is hydrogen, R_{13} and R_{14} are each methyl, R_2 and R_3 , taken together, form an epoxide, and n is 1, the following groups do not occur simultaneously as defined:

(i) R_1 is methyl, R_9 is hydrogen, (R_{11}, R_{12}) is $(=O)$ and R_6 is ethyl or isopropyl;

(ii) R_1 is methyl, R_9 is CHO , (R_{11}, R_{12}) is (OMe, H) and R_6 is ethyl, propyl or isopropyl;

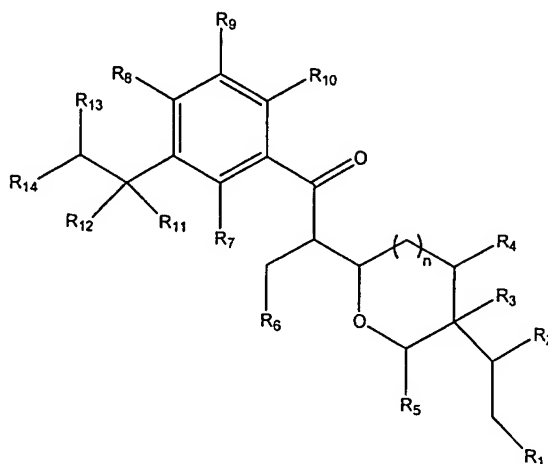
(iii) R_1 is methyl, R_9 is CHO , R_{11} and R_{12} are hydrogen and R_6 is ethyl, propyl or isopropyl;

(iv) R_1 is methyl, R_9 is $COCH_3$, R_{11} and R_{12} are hydrogen and R_6 is ethyl; and

(v) R_1 is ethyl, R_9 is CHO , R_{11} and R_{12} are hydrogen and R_6 is ~~ethyl~~ ethyl; and

(b) when R₁ is methyl, R₂ and R₃, taken together, form an epoxide, R₆ is ethyl, R₇ is hydrogen, (R₁₁, R₁₂) is (OMe, H), R₁₃ and R₁₄ are each methyl and n is 1, the following groups do not occur simultaneously as defined: R₄ and R₅ is OH or OBn, R₈ and R₁₀ is OH or -OCH₂OCH₃ and R₉ is -CHO, -CH₂OH or -CH₂OTBS.

22. A pharmaceutical composition comprising:
a compound having the structure:



and or pharmaceutically acceptable ~~derivatives~~ derivative thereof; and

a pharmaceutically acceptable carrier;

wherein n is 0, 1 or 2;

R₁ is hydrogen or an aliphatic, heteroaliphatic, aryl or heteroaryl moiety;

R₂ and R₃ are each independently hydrogen, or, when taken together, may be -O- or -
(CH₂)_q-, where q is 1, 2 or 3;

R₄ is hydrogen, hydroxyl, protected hydroxyl or ORⁱ, or an aliphatic or heteroaliphatic moiety,

wherein Rⁱ is an aliphatic or heteroaliphatic moiety;

R₅ is hydrogen, hydroxyl, protected hydroxyl or ORⁱⁱ, or an aliphatic or heteroaliphatic moiety,

wherein Rⁱⁱ is an aliphatic or heteroaliphatic moiety, or wherein R₁ and R₅,

when taken together, may form a cycloaliphatic or heterocycloaliphatic moiety comprising 6 to 12 atoms;

R₆ is hydrogen, or an aliphatic, heteroaliphatic, aryl or heteroaryl moiety;

R₇ is hydrogen, hydroxyl, protected hydroxyl, ORⁱⁱⁱ, or an aliphatic or heteroaliphatic moiety,

wherein Rⁱⁱⁱ is an aliphatic or heteroaliphatic moiety;

R₈ is hydrogen, hydroxyl, protected hydroxyl or OR^{iv},

wherein R^{iv} is an aliphatic or heteroaliphatic moiety;

R₉ is hydrogen, -CF₃, -CHO, imine, hydrazone, oxime, carboxylic acid, carboxylic ester, acyl halide, ketone, amide, acetal, anhydride, dihalide, epoxide, nitrile or an aliphatic or heteroaliphatic moiety;

R₁₀ is hydroxyl or protected hydroxyl;

R₁₁ and R₁₂ are each independently hydrogen, hydroxyl or OR^v, or an aliphatic or heteroaliphatic moiety, or, when taken together, may be -(C=O)-;

wherein R^v is an aliphatic or heteroaliphatic moiety;

and R₁₃ and R₁₄ are each independently hydrogen, or an aliphatic, heteroaliphatic, aryl or heteroaryl moiety; and

pharmaceutically acceptable derivatives thereof;

whereby each of the foregoing aliphatic and heteroaliphatic moieties may independently be substituted or unsubstituted, cyclic or acyclic, linear or branched, and whereby each of the foregoing aryl and heteroaryl moieties may be substituted or ~~unsubstituted~~ unsubstituted;

with the proviso that when R₄, R₅, R₈ and R₁₀ are each hydroxyl, R₇ is hydrogen, R₁₃ and R₁₄ are each methyl, R₂ and R₃, taken together, form an epoxide, and n is 1, the following groups do not occur simultaneously as defined:

(i) R₁ is methyl, R₉ is hydrogen, (R₁₁, R₁₂) is (=O) and R₆ is ethyl or isopropyl;

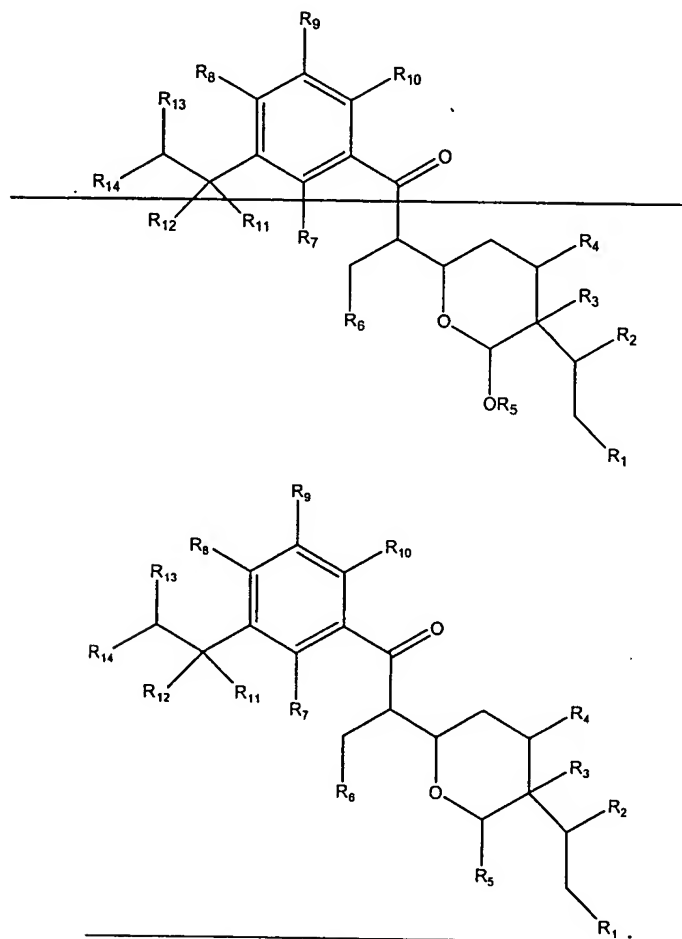
(ii) R₁ is methyl, R₉ is CHO, (R₁₁, R₁₂) is (OMe, H) and R₆ is ethyl, propyl or isopropyl;

(iii) R₁ is methyl, R₉ is CHO, R₁₁ and R₁₂ are hydrogen and R₆ is ethyl, propyl or isopropyl;

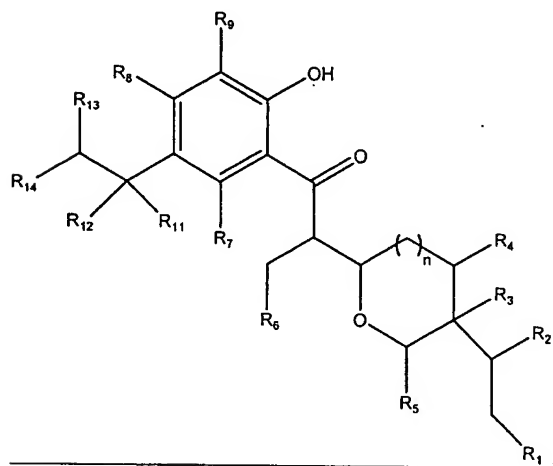
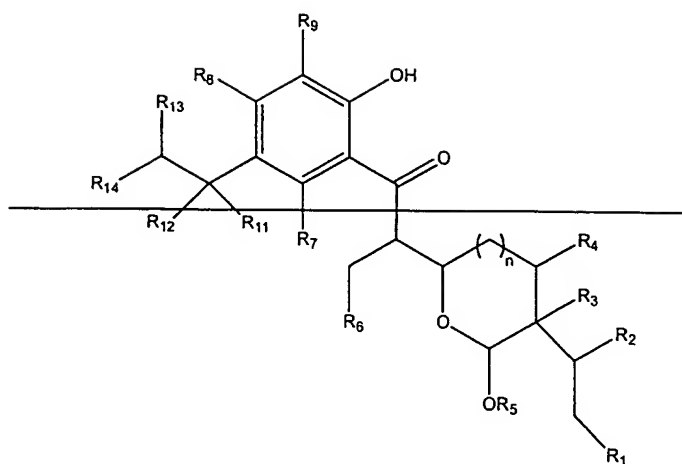
(iv) R₁ is methyl, R₉ is COCH₃, R₁₁ and R₁₂ are hydrogen and R₆ is ethyl; and

(v) R_1 is ethyl, R_9 is CHO, R_{11} and R_{12} are hydrogen and R_6 is ethyl.

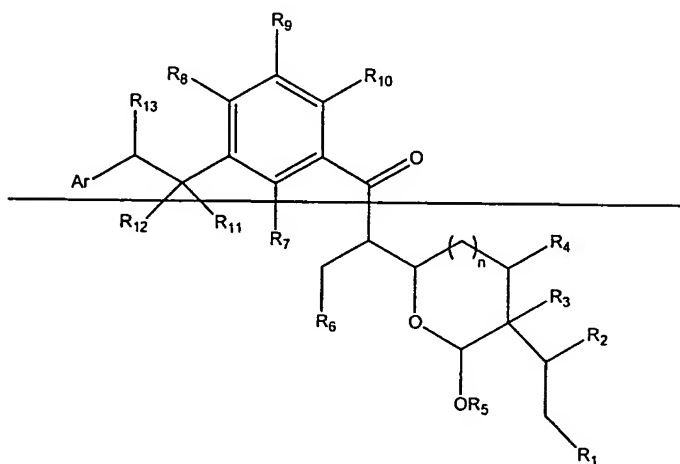
23. The pharmaceutical composition of claim 22 wherein n is 1 and the compound has the structure:

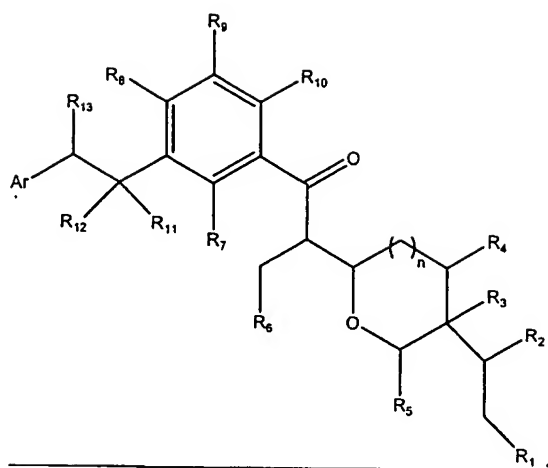


24. The pharmaceutical composition of claim 22 wherein R_{10} is hydroxyl and the compound has the structure:

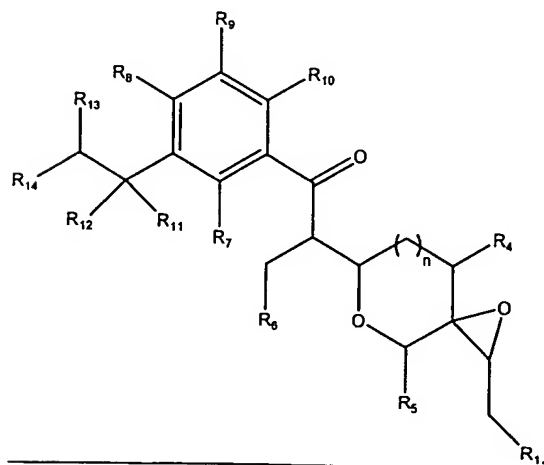
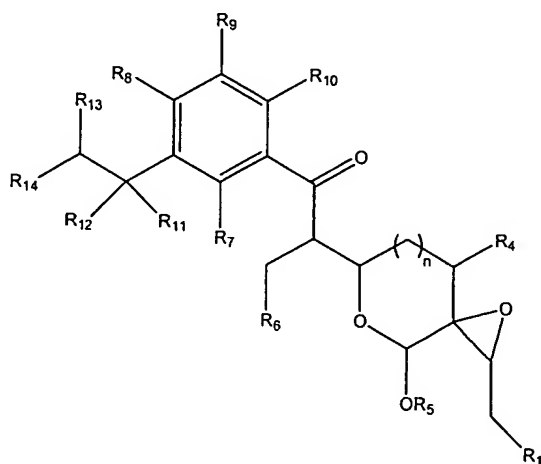


25. The pharmaceutical composition of claim 22 wherein R_{14} is aryl and the compound has the structure:

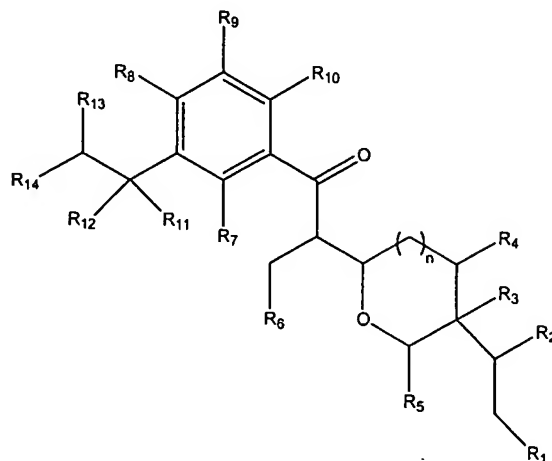




26. The pharmaceutical composition of claim 22 wherein R_2 and R_3 , taken together, form an epoxide, and the compound has the structure:



43. A method for treating cancer comprising:
administering to a subject in need thereof a therapeutically effective amount of a
compound having the structure:



and or pharmaceutically acceptable derivatives derivative thereof;

wherein n is 0, 1 or 2;

R₁ is hydrogen or an aliphatic, heteroaliphatic, aryl or heteroaryl moiety;

R₂ and R₃ are each independently hydrogen, or, when taken together, may be -O- or -
(CH₂)_q-, where q is 1, 2 or 3;

R₄ is hydrogen, hydroxyl, protected hydroxyl or ORⁱ, or an aliphatic or heteroaliphatic
moiety,

wherein Rⁱ is an aliphatic or heteroaliphatic moiety;

R₅ is hydrogen, hydroxyl, protected hydroxyl or ORⁱⁱ, or an aliphatic or
heteroaliphatic moiety,

wherein Rⁱⁱ is an aliphatic or heteroaliphatic moiety, or wherein R₁ and R₅,
when taken together, may form a cycloaliphatic or heterocycloaliphatic moiety
comprising 6 to 12 atoms;

R₆ is hydrogen, or an aliphatic, heteroaliphatic, aryl or heteroaryl moiety;

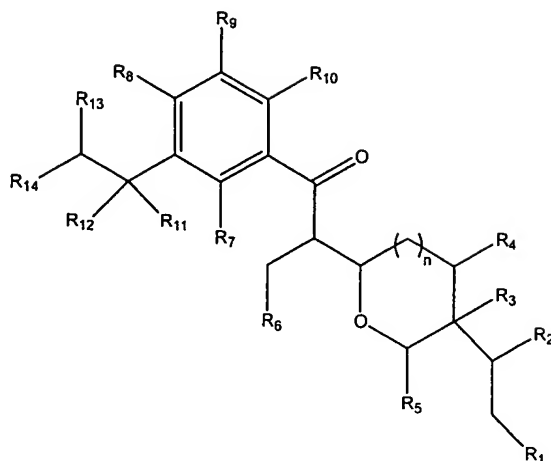
R₇ is hydrogen, hydroxyl, protected hydroxyl, ORⁱⁱⁱ, or an aliphatic or heteroaliphatic
moiety,

wherein R^{iii} is an aliphatic or heteroaliphatic moiety;
 R_8 is hydrogen, hydroxyl, protected hydroxyl or OR^{iv} ,
 wherein R^{iv} is an aliphatic or heteroaliphatic moiety;
 R_9 is hydrogen, $-CF_3$, $-CHO$, imine, hydrazone, oxime, carboxylic acid, carboxylic ester, acyl halide, ketone, amide, acetal, anhydride, dihalide, epoxide, nitrile or an aliphatic or heteroaliphatic moiety;
 R_{10} is hydroxyl or protected hydroxyl;
 R_{11} and R_{12} are each independently hydrogen, hydroxyl or OR^v , or an aliphatic or heteroaliphatic moiety, or, when taken together, may be $-(C=O)-$;
 wherein R^v is an aliphatic or heteroaliphatic moiety;
 and R_{13} and R_{14} are each independently hydrogen, or an aliphatic, heteroaliphatic, aryl or heteroaryl moiety;
 whereby each of the foregoing aliphatic and heteroaliphatic moieties may independently be substituted or unsubstituted, cyclic or acyclic, linear or branched, and whereby each of the foregoing aryl and heteroaryl moieties may be substituted or ~~unsubstituted~~ unsubstituted;
with the proviso that when R_4 , R_5 , R_8 and R_{10} are each hydroxyl, R_7 is hydrogen, R_{13} and R_{14} are each methyl, R_2 and R_3 , taken together, form an epoxide, and n is 1, the following groups do not occur simultaneously as defined:
(i) R_1 is methyl, R_9 is hydrogen, (R_{11}, R_{12}) is $(=O)$ and R_6 is ethyl or isopropyl;
(ii) R_1 is methyl, R_9 is CHO , (R_{11}, R_{12}) is (OMe, H) and R_6 is ethyl, propyl or isopropyl;
(ii) R_1 is methyl, R_9 is CHO , R_{11} and R_{12} are hydrogen and R_6 is ethyl, propyl or isopropyl;
(iv) R_1 is methyl, R_9 is $COCH_3$, R_{11} and R_{12} are hydrogen and R_6 is ethyl; and
(v) R_1 is ethyl, R_9 is CHO , R_{11} and R_{12} are hydrogen and R_6 is ethyl.

SUBSTITUTE SHEETS

Claims

1. A compound having the structure:



or pharmaceutically acceptable derivative thereof;

wherein n is 0, 1 or 2;

R₁ is hydrogen or an aliphatic, heteroaliphatic, aryl or heteroaryl moiety;

R₂ and R₃ are each independently hydrogen, or, when taken together, may be -O- or -(CH₂)_q-, wherein q is 1, 2 or 3;

R₄ is hydrogen, hydroxyl, protected hydroxyl or ORⁱ, or an aliphatic or heteroaliphatic moiety,

wherein Rⁱ is an aliphatic or heteroaliphatic moiety;

R₅ is hydrogen, hydroxyl, protected hydroxyl or ORⁱⁱ, or an aliphatic or heteroaliphatic moiety,

wherein Rⁱⁱ is an aliphatic or heteroaliphatic moiety, or wherein R₁ and R₅, when taken together, may form a cycloaliphatic or heterocycloaliphatic moiety comprising 6 to 12 atoms;

R₆ is hydrogen, or an aliphatic, heteroaliphatic, aryl or heteroaryl moiety;

R₇ is hydrogen, hydroxyl, protected hydroxyl, ORⁱⁱⁱ, or an aliphatic or heteroaliphatic moiety,

wherein Rⁱⁱⁱ is an aliphatic or heteroaliphatic moiety;

R₈ is hydrogen, hydroxyl, protected hydroxyl or OR^{iv},

wherein R^{iv} is an aliphatic or heteroaliphatic moiety;

R₉ is hydrogen, -CF₃, -CHO, imine, hydrazone, oxime, carboxylic acid, carboxylic ester, acyl halide, ketone, amide, acetal, anhydride, dihalide, epoxide, nitrile or an aliphatic or heteroaliphatic moiety;

R₁₀ is hydroxyl or protected hydroxyl;

R₁₁ and R₁₂ are each independently hydrogen, hydroxyl or OR^v, or an aliphatic or heteroaliphatic moiety, or, when taken together, may be -(C=O)-;

wherein R^v is an aliphatic or heteroaliphatic moiety;

and R₁₃ and R₁₄ are each independently hydrogen, or an aliphatic, heteroaliphatic, aryl or heteroaryl moiety;

whereby each of the foregoing aliphatic and heteroaliphatic moieties may independently be substituted or unsubstituted, cyclic or acyclic, linear or branched, and whereby each of the foregoing aryl and heteroaryl moieties may be substituted or unsubstituted;

with the proviso that:

(a) when R₄, R₅, R₈ and R₁₀ are each hydroxyl, R₇ is hydrogen, R₁₃ and R₁₄ are each methyl, R₂ and R₃, taken together, form an epoxide, and n is 1, the following groups do not occur simultaneously as defined:

(i) R₁ is methyl, R₉ is hydrogen, (R₁₁, R₁₂) is (=O) and R₆ is ethyl or isopropyl;

(ii) R₁ is methyl, R₉ is CHO, (R₁₁, R₁₂) is (OMe, H) and R₆ is ethyl, propyl or isopropyl;

(iii) R₁ is methyl, R₉ is CHO, R₁₁ and R₁₂ are hydrogen and R₆ is ethyl, propyl or isopropyl;

(iv) R₁ is methyl, R₉ is COCH₃, R₁₁ and R₁₂ are hydrogen and R₆ is ethyl; and

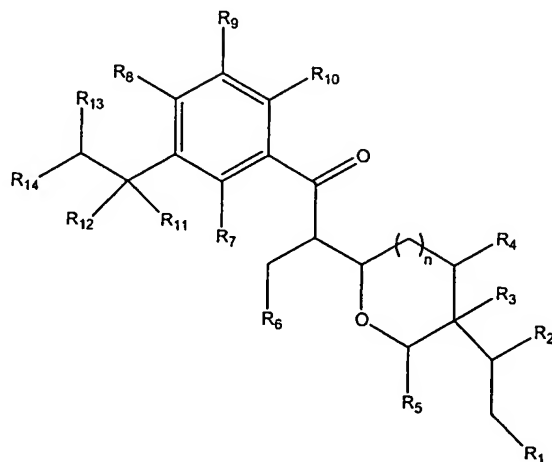
(v) R₁ is ethyl, R₉ is CHO, R₁₁ and R₁₂ are hydrogen and R₆ is ethyl; and

(b) when R₁ is methyl, R₂ and R₃, taken together, form an epoxide, R₆ is ethyl, R₇ is hydrogen, (R₁₁, R₁₂) is (OMe, H), R₁₃ and R₁₄ are each methyl and n is 1, the following groups do not occur simultaneously as defined: R₄ and R₅ is OH or OBn, R₈ and R₁₀ is OH or -OCH₂OCH₃ and R₉ is -CHO, -CH₂OH or -CH₂OTBS.

2. The compound of claim 1 wherein n is 1 and the compound has the structure:

substituted or unsubstituted, branched or unbranched or cyclic or acyclic, and wherein the aryl substituent may be substituted or unsubstituted.

20. The compound of claim 4 or 7 wherein R_{13} is lower alkyl, and wherein the alkyl substituent may be substituted or unsubstituted, linear or branched or cyclic or acyclic.
21. The compound of claim 7 wherein R_1 is hydrogen or lower alkyl, R_5 is hydroxyl or lower alkoxy, R_6 is lower alkyl, R_7 is hydrogen, hydroxyl, lower alkyl or lower alkoxy, R_8 is hydrogen, hydroxyl or protected hydroxyl, R_9 is $-\text{CHO}$ or $-\text{CH}_2\text{OR}^{\text{vi}}$, R_{11} and R_{12} are independently hydrogen or lower alkoxy, and R_{13} is lower alkyl; wherein R^{vi} is hydrogen, protecting group or an aliphatic or heteroaliphatic moiety; whereby each of the foregoing alkyl, alkoxy, aliphatic and heteroaliphatic moieties may be independently substituted or unsubstituted, linear or branched, or cyclic or acyclic.
22. A pharmaceutical composition comprising:
a compound having the structure:



or pharmaceutically acceptable derivative thereof; and

a pharmaceutically acceptable carrier;

wherein n is 0, 1 or 2;

R_1 is hydrogen or an aliphatic, heteroaliphatic, aryl or heteroaryl moiety;

R₂ and R₃ are each independently hydrogen, or, when taken together, may be -O- or -
(CH₂)_q-, where q is 1, 2 or 3;

R₄ is hydrogen, hydroxyl, protected hydroxyl or ORⁱ, or an aliphatic or heteroaliphatic moiety,

wherein Rⁱ is an aliphatic or heteroaliphatic moiety;

R₅ is hydrogen, hydroxyl, protected hydroxyl or ORⁱⁱ, or an aliphatic or heteroaliphatic moiety,

wherein Rⁱⁱ is an aliphatic or heteroaliphatic moiety, or wherein R₁ and R₅, when taken together, may form a cycloaliphatic or heterocycloaliphatic moiety comprising 6 to 12 atoms;

R₆ is hydrogen, or an aliphatic, heteroaliphatic, aryl or heteroaryl moiety;

R₇ is hydrogen, hydroxyl, protected hydroxyl, ORⁱⁱⁱ, or an aliphatic or heteroaliphatic moiety,

wherein Rⁱⁱⁱ is an aliphatic or heteroaliphatic moiety;

R₈ is hydrogen, hydroxyl, protected hydroxyl or OR^{iv},

wherein R^{iv} is an aliphatic or heteroaliphatic moiety;

R₉ is hydrogen, -CF₃, -CHO, imine, hydrazone, oxime, carboxylic acid, carboxylic ester, acyl halide, ketone, amide, acetal, anhydride, dihalide, epoxide, nitrile or an aliphatic or heteroaliphatic moiety;

R₁₀ is hydroxyl or protected hydroxyl;

R₁₁ and R₁₂ are each independently hydrogen, hydroxyl or OR^v, or an aliphatic or heteroaliphatic moiety, or, when taken together, may be -(C=O)-;

wherein R^v is an aliphatic or heteroaliphatic moiety;

and R₁₃ and R₁₄ are each independently hydrogen, or an aliphatic, heteroaliphatic, aryl or heteroaryl moiety; and

pharmaceutically acceptable derivatives thereof;

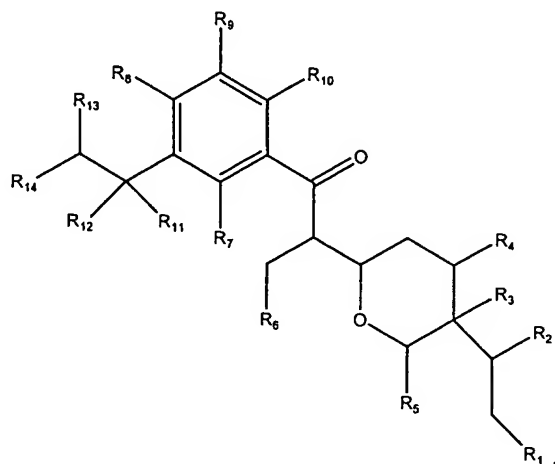
whereby each of the foregoing aliphatic and heteroaliphatic moieties may independently be substituted or unsubstituted, cyclic or acyclic, linear or branched, and whereby each of the foregoing aryl and heteroaryl moieties may be substituted or unsubstituted;

with the proviso that when R₄, R₅, R₈ and R₁₀ are each hydroxyl, R₇ is hydrogen, R₁₃ and R₁₄ are each methyl, R₂ and R₃, taken together, form an epoxide, and n is 1, the following groups do not occur simultaneously as defined:

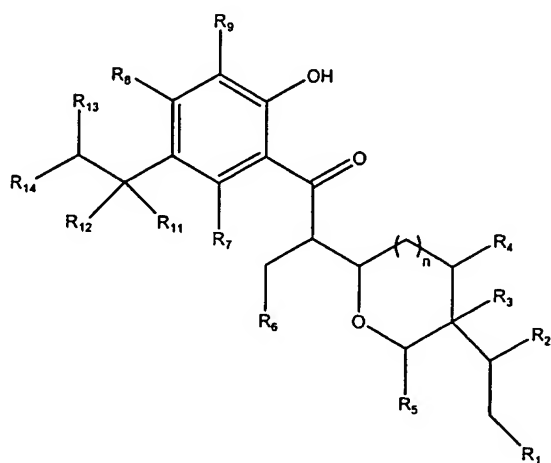
(i) R₁ is methyl, R₉ is hydrogen, (R₁₁, R₁₂) is (=O) and R₆ is ethyl or isopropyl;

- (ii) R_1 is methyl, R_9 is CHO, (R_{11} , R_{12}) is (OMe, H) and R_6 is ethyl, propyl or isopropyl;
- (iii) R_1 is methyl, R_9 is CHO, R_{11} and R_{12} are hydrogen and R_6 is ethyl, propyl or isopropyl;
- (iv) R_1 is methyl, R_9 is COCH₃, R_{11} and R_{12} are hydrogen and R_6 is ethyl; and
- (v) R_1 is ethyl, R_9 is CHO, R_{11} and R_{12} are hydrogen and R_6 is ethyl.

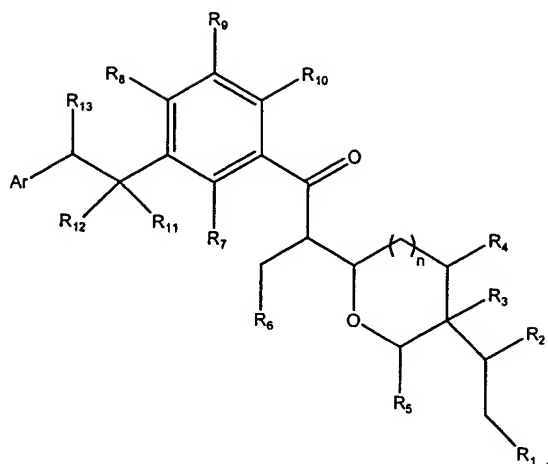
23. The pharmaceutical composition of claim 22 wherein n is 1 and the compound has the structure:



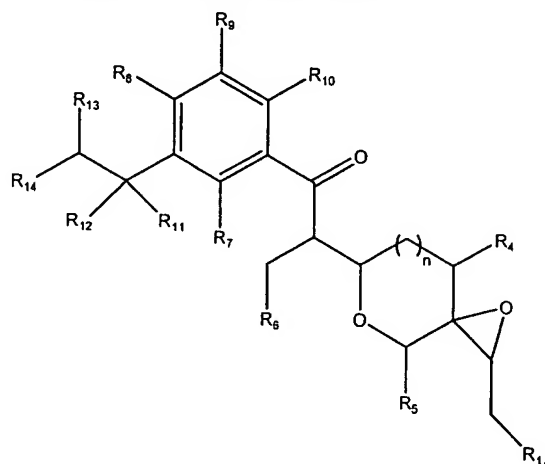
24. The pharmaceutical composition of claim 22 wherein R_{10} is hydroxyl and the compound has the structure:



25. The pharmaceutical composition of claim 22 wherein R_{14} is aryl and the compound has the structure:

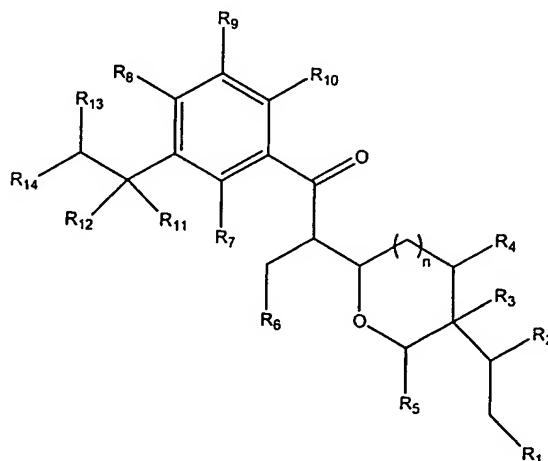


26. The pharmaceutical composition of claim 22 wherein R_2 and R_3 , taken together, form an epoxide, and the compound has the structure:



27. The pharmaceutical composition of claim 22 wherein R_4 is hydroxyl and the compound has the structure:

40. The pharmaceutical composition of any one of claims 22, 23, 24, 26 or 27 wherein R_{13} and R_{14} are independently hydrogen, lower alkyl or aryl, wherein the alkyl substituent may be substituted or unsubstituted, branched or unbranched or cyclic or acyclic, and wherein the aryl substituent may be substituted or unsubstituted.
41. The pharmaceutical composition of claim 25 or 28 wherein R_{13} is lower alkyl, and wherein the alkyl substituent may be substituted or unsubstituted, linear or branched or cyclic or acyclic.
42. The pharmaceutical composition of claim 28 wherein R_1 is hydrogen or lower alkyl, R_5 is hydroxyl or lower alkoxyl, R_6 is lower alkyl, R_7 is hydrogen, hydroxyl, lower alkyl or lower alkoxyl, R_8 is hydrogen, hydroxyl or protected hydroxyl, R_9 is $-CHO$ or $-CH_2OR^{vi}$, R_{11} and R_{12} are independently hydrogen or lower alkoxyl, and R_{13} is lower alkyl; wherein R^{vi} is hydrogen, protecting group or an aliphatic or heteroaliphatic moiety;
- whereby each of the foregoing alkyl, alkoxyl, aliphatic and heteroaliphatic moieties may be independently substituted or unsubstituted, linear or branched, or cyclic or acyclic.
43. A method for treating cancer comprising:
administering to a subject in need thereof a therapeutically effective amount of a compound having the structure:



or pharmaceutically acceptable derivative thereof;

wherein n is 0, 1 or 2;

R₁ is hydrogen or an aliphatic, heteroaliphatic, aryl or heteroaryl moiety;

R₂ and R₃ are each independently hydrogen, or, when taken together, may be -O- or -(CH₂)_q-, where q is 1, 2 or 3;

R₄ is hydrogen, hydroxyl, protected hydroxyl or ORⁱ, or an aliphatic or heteroaliphatic moiety,

wherein Rⁱ is an aliphatic or heteroaliphatic moiety;

R₅ is hydrogen, hydroxyl, protected hydroxyl or ORⁱⁱ, or an aliphatic or heteroaliphatic moiety,

wherein Rⁱⁱ is an aliphatic or heteroaliphatic moiety, or wherein R₁ and R₅, when taken together, may form a cycloaliphatic or heterocycloaliphatic moiety comprising 6 to 12 atoms;

R₆ is hydrogen, or an aliphatic, heteroaliphatic, aryl or heteroaryl moiety;

R₇ is hydrogen, hydroxyl, protected hydroxyl, ORⁱⁱⁱ, or an aliphatic or heteroaliphatic moiety,

wherein Rⁱⁱⁱ is an aliphatic or heteroaliphatic moiety;

R₈ is hydrogen, hydroxyl, protected hydroxyl or OR^{iv},

wherein R^{iv} is an aliphatic or heteroaliphatic moiety;

R₉ is hydrogen, -CF₃, -CHO, imine, hydrazone, oxime, carboxylic acid, carboxylic ester, acyl halide, ketone, amide, acetal, anhydride, dihalide, epoxide, nitrile or an aliphatic or heteroaliphatic moiety;

R₁₀ is hydroxyl or protected hydroxyl;

R₁₁ and R₁₂ are each independently hydrogen, hydroxyl or OR^v, or an aliphatic or heteroaliphatic moiety, or, when taken together, may be -(C=O)-;

wherein R^v is an aliphatic or heteroaliphatic moiety;

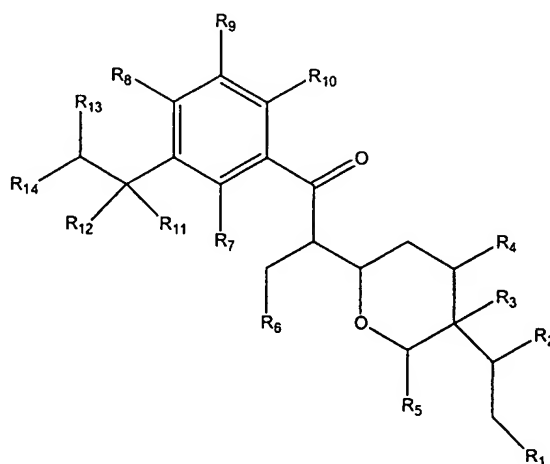
and R₁₃ and R₁₄ are each independently hydrogen, or an aliphatic, heteroaliphatic, aryl or heteroaryl moiety;

whereby each of the foregoing aliphatic and heteroaliphatic moieties may independently be substituted or unsubstituted, cyclic or acyclic, linear or branched, and whereby each of the foregoing aryl and heteroaryl moieties may be substituted or unsubstituted;

with the proviso that when R_4 , R_5 , R_8 and R_{10} are each hydroxyl, R_7 is hydrogen, R_{13} and R_{14} are each methyl, R_2 and R_3 , taken together, form an epoxide, and n is 1, the following groups do not occur simultaneously as defined:

- (i) R_1 is methyl, R_9 is hydrogen, (R_{11}, R_{12}) is $(=O)$ and R_6 is ethyl or isopropyl;
- (ii) R_1 is methyl, R_9 is CHO, (R_{11}, R_{12}) is (OMe, H) and R_6 is ethyl, propyl or isopropyl;
- (iii) R_1 is methyl, R_9 is CHO, R_{11} and R_{12} are hydrogen and R_6 is ethyl, propyl or isopropyl;
- (iv) R_1 is methyl, R_9 is COCH₃, R_{11} and R_{12} are hydrogen and R_6 is ethyl; and
- (v) R_1 is ethyl, R_9 is CHO, R_{11} and R_{12} are hydrogen and R_6 is ethyl.

45. The method of claim 43 wherein in the compound n is 1 and the compound has the structure:



46. The method of claim 43 wherein in the compound R_{10} is hydroxyl and the compound has the structure: